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(54) **Progestational pharmaceutical formulations**

(57) The pharmaceutical formulation providing a progestationally active agent such as medroxyprogesterone acetate together with folic acid is effective in reducing hair loss in men.

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FIG. 1.

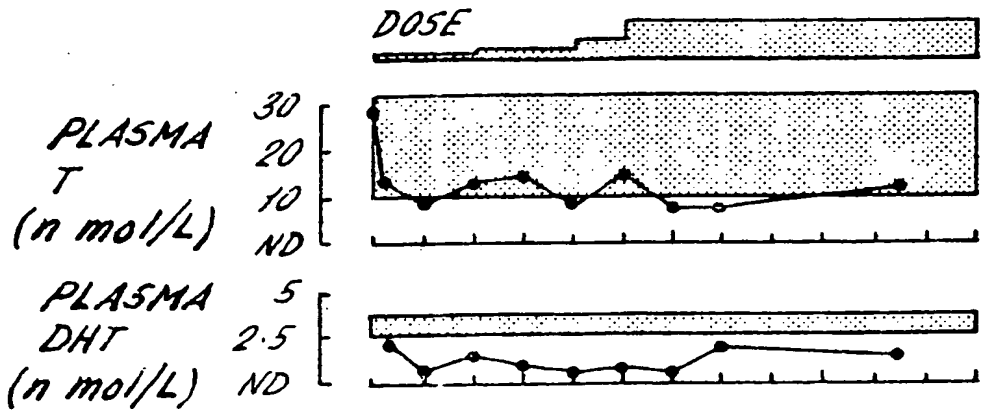
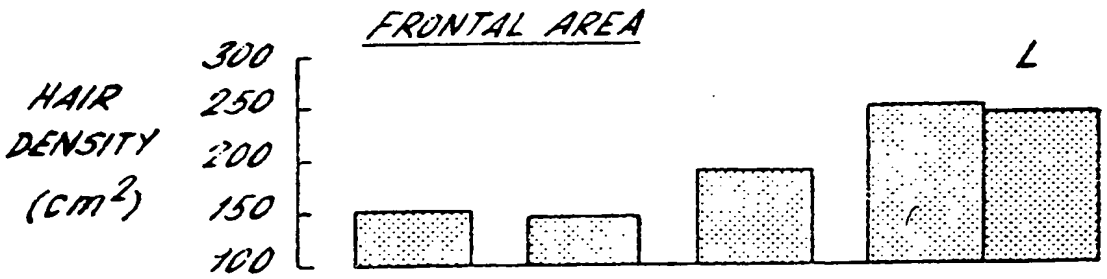


FIG. 2.



SPECIFICATION

Progestational pharmaceutical formulations

The present invention relates to progestational pharmaceutical formulations and to their use, eg. in the treatment of men to reduce hair loss and even to provide an increase in hair growth.

Many men are subject to gradual or rapid natural hair loss, so called Male pattern baldness. It is generally the case that hair is lost from the front and top of the head rather than the back and sides. This has been traced to a difference in susceptibility between hairs in these different areas to the plasma level of testosterone and dihydrotestosterone. Previous attempts to lower testosterone or dihydrotestosterone levels to prevent balding have involved the administration of oestrogens.

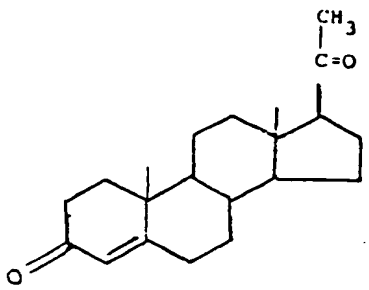
This treatment gave rise to unacceptable side effects such as loss of sexual potency and feminization.

I have now discovered that certain agents can be used to lower the level of plasma dihydrotestosterone without excessive lowering of the level of plasma testosterone.

So long as the plasma testosterone remains within the normal range, sexual potency and spermatogenesis are substantially maintained whilst the overall lowering of testosterone and dihydrotestosterone levels allow those hair follicles which are sensitive to testosterone and dihydrotestosterone to remain active and healthy. Follicles which have already been affected by testosterone and dihydrotestosterone recover and produce normal hair provided that they have not been inactive for a substantial period before treatment.

The preferred agent for use in this treatment is medroxyprogesterone acetate. This is presently marketed under the name PROVERA as a contraceptive for women.

However, I consider compounds having progestational activity generally to be suitable for use in this invention. Progesterone itself is a naturally occuring hormone and has the structure:-



Many synthetic compounds are known which are related to progesterone in structure and exhibit similar hormonal activity. Progestational activity may be defined by the following tests:-

1. *Deciduoma test* - in which young female mice are treated with the substance under test from the 4th to 7th day after spaying. On the 5th day of the test the left uterine horns are damaged by tacking nylon threads through them, and they are examined three days later. If the substance has progestational activity a deciduoma is found in the damaged uterine horn.
2. *The Clauberg test* - in which the endometrium of the infantile female rabbit is brought to the proliferative stage by oestrogens. The substance under test is then examined for its power to transform the endometrium to the secretory stage.

Progestational agents are also thermogenic, cause desquamation of superficial cells of the vaginal mucosa, inhibit ferning of the cervical mucus, induce withdrawal bleeds in oestrogen primed women and female animals and postpone menstruation.

Synthetic progestational compounds are preferred to progesterone itself because progesterone taken orally is eventually degraded to testosterone and dihydrotestosterone.

The main structural feature connection with progestational activity appears to be the 3 keto Δ 4 configuration shown in the above formula. Hormones containing this feature and exhibiting progestational activity include 19-nortestosterone, 17 methyl nortestosterone and antiandrostenedione. However, not all antiandrogen compounds possess this feature and indeed not all such compounds have a steroid structure.

Other conditions are also treatable with progestational agents in general and medroxyprogesterone in particular. Dematalogical problems such as acne vulgaris in men may be treated in this way.

I have observed that many patients for whom progestational agent therapy is appropriate would also benefit from treatment with folic acid. Often their diet is poor through their being in a state of general depression because of their general medical condition. Often also, such patients are in need of new tissue growth or better fertility. Folic acid is appropriate in such cases since it is, together with vitamin B12 required for the synthesis of nucleic acids and is often lacking in a poor diet.

Accordingly, the present invention provides a pharmaceutical formulation providing a progestationally active agent and folic acid or a pharmaceutically acceptable derivative thereof.

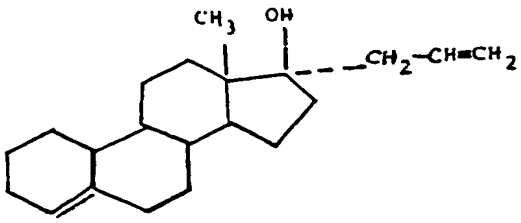
A suitable daily dose rate for folic acid would be 2.5 to 20 mg per day preferably from 5 to 10 mg.

Accordingly, it is preferred that formulations according to this invention contain from 1 to 20 mg per unit

dosage form, more preferably from 2.5 mg to 10 mg, of folic acid or an amount of a derivative thereof which is pharmacologically equivalent.

The invention includes a method of treatment eg of male pattern baldness which comprises administering a progestational agent and a pharmaceutically acceptable source of folic acid. These two active ingredients may be administered separately.

For use in this invention I prefer those synthetic compounds having maximum progestational activity and minimal androgenic activity. Apart from medroxyprogesterone acetate therefore compounds such as allylestrenol, marketed as "Gestanon" by Organon Laboratories, are preferred. The formula of allylestrenol is



Other synthetic progesterone like compounds suitable for use in this invention include the following:-

Gestronol Hexanoate, which is marketing as "Depostat" by Schering AG in the form of an oily solution for intramuscular injection. Ampoules contain 200 mg in 2ml.

Dydrogesterone which is marketed under the name "Duphaston" by Duphar Laboratories as 10 mg tablets.

Norgestrel which is marketed as a combined formulation with conjugated oestrogens under the name "Prempak" by Ayerst.

Norethisterone which is available for instance as 5mg doses under the name "Primolut N" from Schering AG, and

Hydroxyprogesterone hexanoate which is available as 250 mg and 500 mg ampoules under the name "Proluton Depot" from Schering AG.

The use of progesterone itself is not preferred but if progesterone is used, a suitable formulation would be CYCLOGEST which is available either as a 200 mg oral dose or a 400 mg suppository.

Preferably, whichever progesterone like compound is employed is formulated with folic acid or a suitable source thereof to produce a formulation according to the invention.

In reducing hair loss in men the dosage should be so chosen to produce a lowering of plasma dihydrotestosterone level to substantially below the lower limit of the normal range while maintaining plasma testosterone levels at or about the lower limit of the normal male range allowing the retention of potency and fertility. Any agent which produces this effect may be used as the progestational agent.

Preferably, the composition comprises as an active ingredient medroxyprogesterone or a pharmaceutically acceptable derivative thereof, eg an ester such as the acetate.

Preferably, the dosage given is 0.1 to 500 mg of medroxyprogesterone acetate per day by the oral route, more preferably 5 to 40 mg per day. The dose should be selected for the individual patient so that the level of plasma testosterone remains within the normal range whilst that of dihydrotestosterone is significantly depressed. Equivalent doses should preferably be employed where other progestational agents are used.

The composition may be in any of the conventional orally administerable forms such as tablets, capsules, syrups or suspensions. However, the composition may also be designed for topical application eg. it may be formulated as a shampoo, lotion, ointment, cream or alcoholic solution or in any other form suitable for or conveniently employed for topical administration.

The composition may be given by subcutaneous injection into the scalp, or elsewhere, intramuscularly, or intravenously as a depot preparation or not, sublingually, or oral paint, rectally or by any other means of introduction to the body.

The formulations of the present invention may further comprise one or more other diet supplementary agents such as vitamin B12, other vitamins, or trace elements.

For instance, the formulations may include some or all of the following vitamins, preferably in amounts which will provide up to half the normal daily intake of the vitamin concerned which is also shown below.

Vitamin	*Normal Daily Requirement*
Thiamine	0.7 to 0.9mg/day
Pyridoxine (B6)	0.6 to 1.3mg/day
Riboflavin	1 to 1.4mg/day
Vitamin C	10mg/day
Vitamin E activity	3 to 6 Iu/day
Pantothenic acid	5mg/day
Niacin (B3)	9 to 12mg/day

Minerals which may be included include sources of calcium, phosphorus, iodine, iron, magnesium, zinc, copper, cobalt, chromium, manganese, molybdenum and selenium. Again, the formulations are preferably such as to provide up to half the daily requirement of such of the above minerals as are included.

Where the progesterone-like agent and the folic acid are administered separately, different routes may be used for each eg. one may be administered orally and the other topically. For instance, the folic acid optionally with other vitamins or trace elements, may be administered orally and the progesterone like material topically eg. in a shampoo or lotion.

The combination of folic acid and a progesterone-like materials has been found to produce a marked decrease in greasiness of hair in those so treated and this is a further very significant benefit of this treatment.

The normal range for plasma testosterone is 10 to 32 nmol/L. The normal range for plasma dihydrotestosterone is 2.5 to 3.6 nmol/L. I have found that often sufferers from male pattern baldness have a plasma testosterone level which is considerably above the lower limit of normal. This "extra testosterone" is not required for maintaining sexual characteristics but serves to elevate the level of dihydrotestosterone and hence to exacerbate male pattern baldness.

The administration of a synthetic progesterone-like agent such as medroxyprogesterone acetate may reduce circulating testosterone and dihydrotestosterone by several means:

(1) Partial inhibition of hypothalamic gonadotrophin releasing hormone (Gn-RH) secretion.

(2) Partial inhibition of pituitary LH and FSH secretion which are responsible for intratesticular testosterone, dihydrotestosterone, other androgen and oestrogen secretion (LH) and in combination spermatogenesis (FSH).

(3) Partial inhibition of adrenal testosterone, dihydrotestosterone, other androgen and oestrogen secretion, although cortisol secretion in response to stress is not affected since during a glucagon stress test after 42 weeks of treatment plasma cortisol levels rose from 315 nmol/L basally (n170-720) to 775 nmol/L thereby excluding clinically significant hypothalamic-pituitary - ACTH - adrenal - cortisol dysfunction.

(4) Displacement of testosterone from its binding protein SHBG leading to increased clearance and a reduction of substrate for conversion to dihydrotestosterone.

(5) Increased metabolism of testosterone and/or dihydrotestosterone.

(6) Inhibition of the conversion of testosterone to dihydrotestosterone by inhibition of 5a reductase in the liver, testes, other organs, skin and hair follicles.

As a consequence of these actions such an agent will lower circulating and tissue testosterone and dihydrotestosterone levels. A preferential reduction in dihydrotestosterone occurs either in the circulation, or hair follicle or other tissues or in all body compartments. Although there is also some reduction in the testosterone levels this is generally tolerable because levels above the lower limit of the normal male range are surplus to the physiological needs to maintain sexual function.

The growth of hairs may be divided into three phases, the anagen, catagen and telogen phases, corresponding to the stages of growth, stasis and falling. In areas where the hair follicles are susceptible to testosterone or dihydrotesterone there is a shortening of the anagen or growth phase and thus a lower than normal proportion of hairs in the anagen phase. The present invention has been found to produce some degree of return to normal in the distribution of hairs through these phases. The increased growth period implied by this means that more hairs reach a satisfactorily large diameter, increasing the quality of the hair. Also, because hairs that do not grow for a long enough period fall early the average lifetime of the hairs is increased and the rate of hair fall is decreased.

Example

A 25 year old male patient with frontal hair loss and temporal hair recession was selected for treatment. His hair loss had commenced approximately 18 months previously. The basal levels of the patient's plasma testosterone and dihydrotestosterone were measured as well as his sperm count, motility and percentage of abnormal forms. All these parameters were within the normal range. Plasma testosterone was 28.1 nmol/L and dihydrotestosterone was 3.5 nmol/L. The patient's serum folic acid however was found to be at the extreme lower end of the normal range at 2.5 mg/ml.

Treatment with medroxyprogesterone acetate taken orally in combination with folic acid at a level of 5mg/day was commenced. The levels of testosterone and dihydrotestosterone were monitored and the dosage of medroxyprogesterone acetate was varied depending on the results of this monitoring process.

After the first week of treatment, plasma testosterone had fallen to 14.5 nmol/L, well within the normal range of 10 to 32 nmol/L, which plasma dihydrotestosterone had fallen to 1.96 nmol/L, below the normal range of 2.5 to 3.6 nmol/L. During the succeeding 41 weeks of treatment plasma testosterone levels ranged between 8.2 and 15.0 nmol/L, ie generally within the normal range. Dihydrotestosterone levels ranged between 0.21 and 2.21 nmol/L ie. consistently below the normal range.

The patient experienced no loss of libido or potency or decrease in beard growth or body hair growth and there was no gynaecomastia or detectable change in testicular or prostate size. The patient's total sperm count, motility and percentage of abnormal forms were monitored. After 20 weeks of treatment these were less favourable than prior to treatment but the patient was still potentially fertile.

The frontal hair densities 16 weeks prior to the trial and immediately before were 151 and 148 hair/cm^2 respectively. The normal range would be 256 to 393 hairs/cm^2. After 16 weeks the hair density had increased

to 188 hairs/cm^2 and by 42 weeks it was 250 hairs/cm^2. All the measurements were taken from the same frontal area to the right of the midline. A corresponding area to the left of the midline at 42 weeks gave a hair density of 244 hairs/cm^2.

The percentage of hairs in the anagen phase was initially well below the normal range of 84.6 to 93.9% at 39.7%. During treatment this increased to a maximum of 55.3%.

Prior to treatment the percentage of telogen phase hairs was above the normal range of 5.2 to 13.8% at 50.6%. During treatment this decreased to a minimum of 38.3%.

Prior to treatment the percentage of catagen phase hairs was well above the normal range of 0.9 to 2.1% at 9.7% but this fell during treatment to a minimum of 3.2%.

The patient reported an increase in frontal hair and an improvement in hair quality, the hair being "less wispy". This was probably due to an increase in the number of hairs of more than 40 um in diameter from 92 hairs/cm^2 and 90 hairs/cm^2 16 weeks prior to treatment and at time zero respectively (normal range 241 to 340) to 122 hairs/cm^2 after 16 weeks and 142 hairs/cm^2 after 42 weeks of treatment.

Accordingly, it can be seen that a substantial increase in hair density and hair quality was achieved without the patient experiencing any undesirable side effects.

Figure 1 shows the plasma levels of testosterone and dihydrotestosterone during this trial. Figure 2 shows the change in frontal hair density during the trial. No significant changes in occipital hair density were observed.

The patient's serum folic acid level was checked after 2 months of treatment and was found to have risen to more than 20ng/ml indicating that absorption had taken place.

CLAIMS

1. A pharmaceutical formulation providing a progestationally active agent and folic acid or a pharmaceutically acceptable derivative thereof.
2. A formulation as claimed in claim 1 wherein the progestationally active agent is medroxyprogesterone or a pharmaceutically acceptable derivative thereof.
3. A formulation as claimed in claim 2 wherein the progestationally active agent is medroxyprogesterone acetate.
4. A formulation as claimed in any one of claims 1 to 3 in a unit dosage form, each dose providing from 1 to 20 mg of folic acid.
5. A formulation as claimed in claim 4 wherein each dose provides from 5 to 10 mg of folic acid.
6. A formulation as claimed in claim 4 or claim 5 containing from 0.05 to 500 mg of medroxyprogesterone acetate or a pharmacologically equivalent amount of another progestational agent.
7. A formulation as claimed in claim 6 containing from 2.5 to 40 mg of medroxyprogesterone acetate.
8. A formulation as claimed in any preceding claim in the form of a tablet, capsule, sachet or dragee in a form suitable for parenteral administration.
9. A formulation as claimed in any one of claims 1 to 3 in a form suitable for topical application.
10. A formulation as claimed in claim 9 in the form of a lotion, shampoo, ointment or cream.

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